REFERENCES

(1) Christen, A.G., Swanson, B.B., Glover, E.D., and Henderson, A.H. Smokeless tobacco: The folklore and social history of snuffing, sneezing, dipping, and chewing. J. Am. Dent. Assoc. *105:* 821-829, 1982.

(2) Schuman, L.M. Patterns of smoking behavior. In: M.E. Jarvick, J.W. Cullen, E.R. Critz, T.M. Vogt, and L.J. West (eds.). Research on smoking behavior (NIDA Research Monograph 17). U.S. Government Printing Office (Stock No. 017-024-00694-7), 1977.

(3) Shelton, A. Smokeless sales continue to climb. Tobacco Reports, p. 42, August 1982.

(4) Maxwell, J.C., Jr. Chewing, snuff is growth segment. Tobacco Reports, p. 31, September 1980.

(5) Winn, D.M. Tobacco chewing and snuff dipping: An association with human cancer. In: I.K. O'Neil, R.C. Borstel, C.T. Miller, J. Long, and H. Bartsch (eds.). N-Nitroso Compounds Occurrence, Biological Effects and Relevancy to Human Cancers. IARC Scientific Publication No. 57, Oxford University Press, 1985.

(6) Rosenfeld, L., and Callaway, J. Snuff dipper's cancer. Am. J. Surg. *106:* 840-844, 1963.

(7) Agricultural Market Service. Tobacco in the United States. U.S. Department of Agriculture (Miscellaneous Publication No. 867), 1979.

(8) Davis, D.L. Smokeless tobacco products and their production in the United States. Presented at the NIH Consensus Development Conference on the Health Implications of Smokeless Tobacco Use, Bethesda, Maryland, January 13-15, 1986, and personal correspondence.

(9) Bantle, L.F. Smokeless tobacco—A trend to watch. Tabak J. Int. *4:* 344-346, 1980.

(10) Rizio, D. Smokeless tobacco. Tabak J. Int. *2:* 183-184, 1984.

(11) U.S. Department of Agriculture, Economic Research Service. Tobacco: Outlook and Situation Report. Washington, D.C., 1985.

(12) U.S. Department of Agriculture, Agricultural Marketing Service. Annual report on tobacco statistics, 1973. (Statistical Bulletin No. 528). Washington, D.C., 1974.

(13) U.S. Department of Agriculture, Agricultural Marketing Service. Annual report on tobacco statistics, 1976. (Statistical Bulletin No. 570). Washington, D.C., 1977.

(14) U.S. Department of Agriculture, Agricultural Marketing Service. Annual report on tobacco statistics, 1981. (Statistical Bulletin No. 685). Washington, D.C., 1982.

(15) U.S. Department of Agriculture, Agricultural Marketing Service. Tobacco stocks, as of January 1, 1983. Washington, D.C., 1983.

(16) U.S. Department of Agriculture, Agricultural Marketing Service. Tobacco stocks, as of January 1, 1984. Washington, D.C., 1984.

(17) U.S. Department of Agriculture, Agricultural Marketing Service. Tobacco stocks, as of January 1, 1986. Washington, D.C., 1986.

(18) National Clearinghouse for Smoking and Health. Use of tobacco: Practices, attitudes, knowledge, and beliefs. U.S. Fall 1964 and Spring 1966, July 1967.

(19) U.S. Department of Health, Education, and Welfare. Smoking and health—A report to the Surgeon General. Office on Smoking and Health (DHEW Publication No. PHS 79-50066), 1979.

(20) National Clearinghouse for Smoking and Health. Adult use of tobacco, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, 1976.

(21) National Center for Health Statistics. National Health Interview Survey, 1970 (unpublished).

(22) Simmons Market Research Bureau, Inc. Study of Media and Markets, 1980-1985.

(23) Simmons Market Research Bureau, Inc. Simmons National College Study, 1983 and 1985.

(24) Office on Smoking and Health. Current Population Survey, 1985 (unpublished).

(25) Rouse, B.A. National prevalence of smokeless tobacco use. Presented at the NIH Consensus Development Conference on the Health Implications of Smokeless Tobacco Use, Bethesda, Maryland, January 13-15, 1986.

(26) U.S. Department of Commerce, Bureau of the Census. (CP Series P25, No. 922), 1982.

(27) Hartge, P., Hoover, R., and Kantor, A. Bladder cancer risk and pipes, cigars, and smokeless tobacco. Cancer *55:* 901-906, 1985.

(28) Glover, E.D., O'Brien, K., and Holbert, D. Prevalence of smokeless tobacco use in Pitt County, North Carolina. Int. J. Addict. (in press).

(29) Gritz, E.R., Ksir, C., and McCarthy, W.J. Smokeless tobacco use in the United States: Past and future trends. Ann. Behav. Med. *7:* 24-27, 1985.

(30) Glover, E.D., Johnson, R., Laflin, M., and Christen, A. Smokeless tobacco trends in the United States. World Smoking and Health (in press).

(31) Marty, P.J., McDermott, R.J., Young, M., and Guyton, R. Prevalence and psychosocial correlates of dipping and chewing in a group of rural high school students. Health Educ. (in press).

(32) Marty, P.J., McDermott, R.J., and Williams, T. Patterns of smokeless tobacco use in a population of high school students. Am. J. Public Health *76:* 190-192, 1986.

(33) Newman, I.M., and Duryea, E.J. Adolescent cigarette smoking and tobacco chewing in Nebraska. Nebr. Med. J. *66:* 243-244, 1981.

(34) Bonaguro, J.A., Pugy, M., and Bonaguro, E.W. Multivariate analysis of smokeless tobacco use by adolescents in grades four through twelve. Health Educ. (in press).

(35) Lichtenstein, E., Severson, H.H., Friedman, L.S., and Ary, D.V. Chewing tobacco use by adolescents: Prevalence and relation to cigarette smoking. Addict. Behav. (in press).

(36) Severson, H., Lichtenstein, E., and Gallison, C. A pinch or a pouch instead of a puff? Implications of chewing tobacco for addictive processes. Bulletin of Psychologists in Addictive Behaviors *4*: 85-92, 1985.

(37) Jones, R.B. Smokeless tobacco: A challenge for the 80's. Journal of the Wisconsin Dental Association *10:* 717-721, 1985.

(38) Chassin, L., Presson, C.C., and Sherman, S.J. Stepping backward in order to step forward: An acquisition oriented approach to primary prevention. J. Consult. Clin. Psychol. (in press).

(39) Chassin, L., Presson, C.C., Sherman, S.J., McLaughlin, L., and Gioia, D. Psychological correlates of adolescent smokeless tobacco use. Addict. Behav. (in press).

(40) Greer, R.O., and Poulson, T.C. Oral tissue alterations associated with the use of smokeless tobacco by teenagers, I. Clinical findings. Oral Surg. *56:* 275-284, 1983.

(41) Poulson, T.C., Lindenmuth, J.E., and Greer, R.O. A comparison of the use of smokeless tobacco in rural and urban teenagers. CA *34:* 248-261, 1984.

(42) Hunter, S.M., Croft, J.B., Burke, G.L., Parker, F.C., Webber, L.S., and Berenson, G.S. Longitudinal patterns of cigarette smoking and smokeless tobacco use in youth. Am. J. Public Health *76:* 193-195, 1986.

(43) Guggenheimer, J., Zullo, T.G., Krupee, D.C., and Verbin, R.S. Changing trends of tobacco use in a teenage population in western Pennsylvania. Am J. Public Health *76:* 196-197, 1986.

(44) Schaefer, S.D., Henderson, A.H., Glover, E.D., and Christen, A.G. Patterns of use and incidence of smokeless tobacco consumption in school-age children. Arch. Otolaryngol. (in press).

(45) Young, M., and Williamson, D. Correlates of use and expected use of smokeless tobacco among kindergarten children. Psychol. Rep. *56:* 63-66, 1985.

(46) Boyd, G.M., et al. Use of smokeless tobacco among children and adolescents in the United States. Prev. Med. (in press).

(47) Evans, R.I., Hansen, W.G., and Mittelmark, M.B. Increasing the validity of self-reports of smoking behavior in children. J. Appl. Psychol. *62:* 521-523, 1977.

(48) Murray, D.M., O'Connell, C.M., Schmiel, L.A., and Perry, C.P. The validity of smoking self-reports by adolescents: A reexamination of the logic and pipeline procedure. Addict. Behav. (in press).

(49) Bauman, K.E., and Dent, C.W. Influence of an objective measure on self-reports of behavior. J. Appl. Psychol. *67:* 623-638, 1982.

(50) Office of the Inspector General. Youth use of smokeless tobacco: More than a pinch of trouble. U.S. Department of Health and Human Services, January 1986.

Chapter 2.

CARCINOGENESIS ASSOCIATED WITH SMOKELESS TOBACCO USE

CONTENTS

INTRODUCTION

This chapter presents the results of a systematic review of the world's medical literature describing experimental and human evidence pertinent to the evaluation of smokeless tobacco as a potential cause of cancer. Five categories of research relevant to assessing the role of smokeless tobacco in cancer causation were defined:

1. Epidemiologic studies and case reports of oral cancer in relation to smokeless tobacco use.
2. Epidemiologic studies of other cancers in relation to smokeless tobacco use.
3. Chemical constituents of smokeless tobacco.
4. Metabolism of constituents of smokeless tobacco.
5. Experimental studies involving exposing laboratory animals to smokeless tobacco or its constituents.

Consensus summaries of the literature in each of these categories were prepared and form the basis of this report. In addition, recommendations for future rsearch to clarify suggestive findings or fill gaps in knowledge are made.

EPIDEMIOLOGIC STUDIES AND CASE REPORTS OF ORAL CANCER IN RELATION TO SMOKELESS TOBACCO USE

Because smokeless tobacco products used in different regions of the world vary considerably in composition and usage patterns, this section will consider North American and European data separately from Asian data. Citations to the literature from India and other Asian countries where quids containing tobacco and other ingredients are commonly used orally focus on articles that attempt to distinguish tobacco from other ingredients in the quids as possible determinants of cancer risk.

Data From North America and Europe

Although about a dozen informative epidemiologic studies of smokeless tobacco use and oral cancer in North America or Europe have been reported, only a few were specifically designed to examine this relation. There are two major reasons for the relative paucity of studies. Apart from the recent increased prevalence in use of smokeless tobacco, the habit has not been widely practiced in America during this century, except in localized areas such as parts of the rural South *(1,2)*. Furthermore, cancer of the mouth is uncommon in the Western Hemisphere,

exacerbating the difficulty of conducting epidemiologic investigations, particularly cohort studies, into the relation between smokeless tobacco and oral cancer. The age-adjusted incidence rate for cancers of the buccal cavity and pharynx in the United States is approximately 11 cases per 100,000 population per year, with these tumors accounting for about 3 percent of all cancer deaths *(3)*. Nevertheless, sufficient information is available to evaluate whether the use of smokeless tobacco increases the risk of oral cancer.

Case Studies

In their review of 566 oral cancer patients treated in two hospitals in Nashville, Rosenfeld and Callaway *(4,5)* noted that the proportion of women (61 percent) with buccal and gingival carcinoma was higher than the proportion of men (36 percent). Approximately 90 percent of women with buccal and gingival carcinoma used snuff for 30 to 60 years; in contrast, 22 percent of women with cancers in other oral cavity subsites used snuff. Many of these women began practicing "snuff dipping," namely, the placement of tobacco snuff in the gingivobuccal sulcus, between the ages of 10 to 20 years. These reports are typical of numerous and sometimes large series of cases from the South, which reported that high percentages of patients with gingivobuccal cancers were snuff dippers or tobacco chewers *(6-13)*. The articles describing these case series generally did not use comparison (control) groups, but the authors consistently commented on an apparently high prevalence of the use of snuff by the cancer patients. Clinicians also noted that the usual male predominance for epidermoid carcinomas of the oral cavity diminished or disappeared for the subgroup of gingivobuccal carcinomas occurring in geographic areas where there was relatively common use of snuff and chewing tobacco.

Ahblom reported in the 1930's on a possible association between smokeless tobacco and cancer in Sweden *(14)*. Among male patients with cancers of various sites seen at the Radiumhemmet (Stockholm), the use of snuff or chewing tobacco was reported in 70 percent with buccal, gingival, and "mandibular" cancers as compared to 26 to 37 percent with cancers in other oral subsites, the larynx, pharynx, and esophagus. Axéll et al. reviewed medical records of male patients with squamous cell carcinoma in the oral cavity diagnosed between 1962 and 1971 and recorded in the Register of the Swedish Board of Health and Welfare *(15)*. The authors were only able to determine a history for the pattern of use of snuff in 25 percent of eligible patients but commented that two-thirds of patients who were verified snuff users had oral cancers in regions where the snuff was generally placed. Reports of a single or a few cases, usually among male tobacco chewers, in the Northern United States and Canada also described buccal carcinomas that were often located precisely in the area where the tobacco was retained in the mouth *(16-19)*.

In the early 1940's, Friedell and Rosenthal associated the use of snuff or chewing tobacco with an exophytic, verrucous type of squamous carcinoma of the oral cavity *(16)*. Ackerman described in detail the morphologic and clinical features of verrucous carcinoma of the oral cavity *(20)*. Where the lesions originated in the buccal mucosa, a history of chronic use of chewing tobacco was elicited in 60 percent of the patients. The morphologic description was that of a well-differentiated, locally invasive, papillary squamous carcinoma, often in association with leukoplakia. In more than half of these patients, there was poor oral hygiene and carious and missing teeth.

In summary, clinical and pathological reports published during the past four decades in the United States and elsewhere have commented on the use of smokeless tobacco by oral cancer patients and have described the entity known as snuff-dipper's carcinoma *(4,7,11)*, providing the basis for the hypothesis that the prolonged use of snuff or chewing tobacco is associated with an increased risk of low-grade, verrucal or squamous cell carcinoma of the buccal mucosa and gingivobuccal sulcus.

Case Control Studies

Most of the epidemiologic evidence comes from several case-control studies of oral cancer. The low prevalence of smokeless tobacco use in most North American populations contributes to a low statistical efficiency in most of these studies. Good information has been obtained, however, from studies that were either very large, conducted in an area of high prevalence of smokeless tobacco use, or analyzed according to site within the oral cavity (since the tissue affected by snuff use appears to be highly localized). One study, by Winn et al., with these characteristics consequently provides the most informative body of data on the carcinogenicity of smokeless tobacco in North America *(21)*.

The major concern for validity in the epidemiologic studies of smokeless tobacco and oral cancer is uncontrolled confounding. A small number of subjects in crucial categories prevented efficient adjustment for confounding by stratification in many of these studies. Many of the studies were conducted before the advent of sophisticated epidemiologic analyses and make no attempt to control confounding. The two primary confounding factors of concern are alcohol consumption and smoking *(22)*. Alcohol consumption is a strong risk factor for oral cancer. It is not clear on a priori grounds, however, to what extent alcohol consumption would be correlated with smokeless tobacco use. The relation between smoking, also a strong risk factor for oral cancer *(2)*, and smokeless tobacco use may be complex. Users of smokeless tobacco may be more likely to have been smokers at some time. On the other hand, heavy users of smokeless tobacco typically cannot be heavy users of cigarettes, so that smoking is presumably negatively correlated with smokeless tobacco use. Failure to control confounding by smoking would therefore lead to underestimates of the effect of smokeless tobacco.

TABLE 1.—Smokeless Tobacco and Mouth Cancer, Case-Control Data From Moore et al. *(23,24)*

Smokeless Tobacco	Mouth Cancer Cases	Controls
Users	26	12
Nonusers	14	26
Totals	40	38
Crude RR = 4.0	95%-Confidence Interval:	1.6—10

Chronologically, the first case-control study of smokeless tobacco was conducted by Moore et al. in Minnesota (23,24). Patients at the University of Minnesota Tumor Clinic with a diagnosis of cancer of the mouth were interviewed about tobacco use as part of a general interview procedure for clinic patients. Surgical outpatients who received the same interviews served as controls. From the data that were reported by these authors, one can calculate a crude relative risk estimate for mouth cancer among smokeless tobacco users of 4.0 with a 95-percent confidence interval of 1.6-10 (table 1). An oddity was an apparent lack of effect for other forms of tobacco use. A partial explanation might be negative confounding between smokeless and smoked tobacco; indeed, 26 of the 40 cases of mouth cancer chewed tobacco. Still, the extent of disparity in crude effect estimates for smokeless tobacco (relative risk estimate 4.0) and smoked tobacco (all relative risk estimates < 1.0) is surprising.

Wynder et al. reported on a case-control study of squamous cell cancers of the upper alimentary and respiratory tract that was conducted at Sweden's Radiumhemmet in 1952-55, including 33 tongue cancer patients, 14 lip cancer patients, 19 gingival cancer patients, and 8 patients with cancer of the buccal mucosa, among others (25). Controls were patients with cancers of the skin, head, and neck other than squamous cell carcinoma, stomach cancer, lymphoma, salivary-gland tumors, leukemia, sarcoma, cancers of the colon and rectum, and cancers of the female genital tract. A variety of risk factors was examined, including the use of chewing tobacco. The authors state that the data suggested that an increased risk is associated with the duration of chewing tobacco for cancers of the gingiva and oral cavity but not for cancers of the tongue, lip, hypopharynx, esophagus, or larynx, but the data as presented do not permit an estimation of risk. In addition, data were not adjusted for other potential confounders, including cigarette smoking. Wynder and colleagues also reported in 1957 data from a similar hospital-based case-control study of mouth cancer conducted in New York *(26)*. Tobacco chewing was found to be more common among men with oral cavity cancers than among controls; but it was noted that almost all of these patients also drank alcoholic beverages and smoked, and no further analyses were attempted.

TABLE 2.—Smokeless Tobacco and Mouth Cancer, Case-Control Data From Peacock et al. *(27)*

Smokeless Tobacco	Age					
	40-49		50-59		60-69	
	Case	Controls	Case	Controls	Case	Controls
User	0	16	7	13	18	20
Nonuser	5	14	6	16	9	37
Total	5	60	13	29	27	57
	RR = 0		RR = 1.4		RR = 3.7	
	RRMH = 2.0		95%-Confidence Interval: 1.0—4.2			

Peacock et al. studied 56 cases of mouth cancer, including malignancies of the buccal mucosa, alveolar ridge, and floor of the mouth, and compared their tobacco histories with those of two control groups: 146 hospitalized controls with diagnoses other than cancer and 217 outpatients *(27)*. Age-specific results using the hospitalized controls are summarized in table 2. The overall relative risk was estimated to be 2.0 (95-percent confidence interval 1.0-4.2); the relative risk seemed to increase with age with an estimate of 3.7 for the 60 to 69 age group. The data were not reported in sufficient detail to control for confounding by smoking, which presumably led to underestimates of the relative risk. There was also insufficient detail reported to evaluate the relation between the risk of mouth cancer and the amount or duration of smokeless tobacco use.

In Atlanta, patients with oral, pharynx, and larynx cancer were compared to three control groups having other mouth diseases, other cancers, or no cancer *(28)*. Among urban women, 40 percent of the cases used snuff compared to 3 percent or less of the controls (table 3). Among rural women, 75 percent dipped snuff compared to 20 percent or less among controls. Cigarette smoking was common in urban women and not specifically controlled for. Few rural female cases smoked cigarettes (7 percent) so confounding by smoking was minimal. The association between snuff dipping and oral, pharynx, and larynx cancer in women was generally evident in most age groups. Among the cases, the proportion of snuff dippers was highest among oral cancer patients: 53/72 were dippers compared to 2/18 pharynx and larynx cancer patients. Among men, insufficient information was provided to obtain precise epidemiologic estimates of the effect of chewing tobacco, although data from one of the bar charts presented indicate that urban cases were more likely to be users of smokeless tobacco than controls, that rural men with oral, pharynx, and larynx cancer or mouth disease were more likely to chew than controls, and that oral cancer patients were more likely to chew

TABLE 3.—Estimated Relative Risks Associated With Snuff Use for Cancers of the Oral Cavity, Pharynx, and Larynx, Case-Control Data From Vogler et al. *(28)*, Females Only

	Oral/ Pharynx/ Larynx	Other Mouth Disease	Other Cancer	No Cancer
Urban				
User	15	1	5	4
Nonuser	23	56	165	373
Crude Relative Risk Estimate	60.8	1.7	2.8	1.0*
Rural				
User	41	4	26	17
Nonuser	14	33	103	133
Crude Relative Risk Estimate	22.9	0.9	2.0	1.0*

* Reference category.

TABLE 4.—Smokeless Tobacco and Head and Neck Cancer by Anatomic Site, Case-Control Data From Vincent and Marchetta *(29)*, Males Only

Smokeless Tobacco Use	Control	Larynx	Pharynx	Oral Cavity	All Head and Neck
User	5	2	3	9	14
Nonuser	95	21	30	24	75
Total	100	23	33	33	89
Relative Risk Estimate		1.8	1.9	7.1	3.5
95%-Confidence Interval		0.3—9.8	0.4—8.3	2.4—21	1.3—9.8

than the pharynx and larynx cancer cases. Among men, confounding by smoking could not be ruled out.

Vincent and Marchetta reported the results of a case-control study of head and neck cancer according to anatomic site. Table 4 summarizes the findings for males *(29)*. The oral cavity seems to be the anatomic site where the bulk of the effect is noted; only mild increases in risk were estimated for the larynx and pharynx, whereas users of smokeless tobacco were estimated to have a sevenfold greater risk for cancer of the oral cavity. These estimates are imprecise because of the small number of subjects and are uncontrolled for age and smoking.

TABLE 5.—Estimated Relative Risk for Cancer of the Head and Neck From Smokeless Tobacco Use by Anatomic Site, Third National Cancer Survey (31), Males Only

Anatomic Site	Relative Risk Estimate	
	Low Exposure	High Exposure
Gum-Mouth	5.6	3.9
Pharynx	0.6	—
Lip-Tongue	0.3	1.1
Larynx	2.0	1.7

Martinez reported on a case-control study in Puerto Rico of risk factors for cancers of the mouth, pharynx, and esophagus *(30)*. This population-based study included 400 cases of epidermoid carcinomas of those sites and 1,200 controls matched on age (±5 years) and sex to the cases. One control per case was drawn from the same hospital or clinic and two from the same community. There were 153 cases of mouth cancer (115 male and 38 female) and 68 cases of pharyngeal cancer (55 male and 13 female). The authors concluded that "Patients with cancer of the mouth did not often use chewing tobacco disproportionately . . ." However, calculation of the relative risks of mouth cancer that are associated with chewing tobacco based on comparing the use of chewing tobacco only with no tobacco use suggests a strong effect for oral and pharyngeal cancer in males (data from table 13 in the paper). The estimated relative risks were 11.9 (95-percent confidence interval 2.5-56.4) for oral cancer and 8.7 (95-percent confidence interval 1.4-54.5) for pharyngeal cancer among chewers. These numbers do not include the experience of the many study subjects whose use of tobacco was "mixed" (that is, those who used any combination of cigarette, cigar, and pipe smoking and chewing tobacco), and these calculations were based on unmatched data.

Further evidence for the site specificity arose from a case-control analysis of multiple cancers using data from the Third National Cancer Survey *(31)*. There were few female users of smokeless tobacco and scanty data by site within the head and neck region even for males; the findings do seem to indicate that the effect is greater for the site that is labeled gum-mouth as opposed to other head and neck sites (table 5).

Browne et al. conducted interviews with 75 oral cancer patients, or (usually) their next of kin, and 150 living sex-, neighborhood-, and occupation-matched controls in the West Midlands area of the United Kingdom where oral cancer mortality rates were high and tobacco chewing was common among miners *(32)*. Controls on average were born about 10 years earlier than the cases. The proportion of tobacco chewers was approximately the same among the 16 cases and 43 con-

trols who were miners, although data on this variable were missing for one-fourth of the cases, and the authors apparently assumed that all cases with missing information were nonchewers. If the proportion of tobacco chewers among the cases with missing information was similar to those miners with known information, then the data would have shown a positive association between chewing tobacco and oral cancer. All of the miners with oral cancer who chewed tobacco also smoked pipes, further complicating interpretation of this study.

Additional evidence that a carcinogenic effect of smokeless tobacco may be greatest at the anatomic site of exposure came from Westbrook et al. who compared the medical records of 55 female patients with cancers of the alveolar ridge or buccal mucosa who were treated at the University of Arkansas with those of 55 randomly selected female hospital controls *(33)*. Fifty of the cases, but only one control, were snuff dippers, with the tumors among the cases typically appearing at the site where the snuff was usually placed. No reliable estimates of risk can be derived from this study because of the strong possibility that there was not comparable elicitation of exposure information for cases and controls.

Two large case-control studies were not reported in a way that enables a meaningful quantitative assessment of the effect of smokeless tobacco in chewers and dippers compared to tobacco abstainers *(34,35)*. The first study found that 10 percent, and the second 9 percent, of male oral cancer cases had ever chewed tobacco, while the corresponding figure for controls was 9 percent. These studies, like many of the others cited here, were not undertaken specifically to evaluate the carcinogenicity of smokeless tobacco. Although the data seem to indicate a weak relation, if any, between smokeless tobacco and cancer of the oral cavity, the findings are uncontrolled for age, race, geography, and smoking.

The recent case-control study of Winn et al. is by far the most informative study on the carcinogenicity of smokeless tobacco *(21)*. The case series comprised 255 women with oral and pharyngeal cancer who were living in 67 counties in a high-risk (for oral cancer) region of North Carolina. Two female controls were obtained for all but a few cases and were individually matched for age, race, source of ascertainment (hospital or death certificate), and county of residence. There was a fourfold increased risk of oral-pharyngeal cancer among nonsmoking white women who dipped snuff. The association could not be explained by smoking or alcoholic beverage consumption *(21)*, denture wearing or poor dentition *(36)*, diet *(37)*, or mouthwash use *(38)*. The data provided evidence for a strong relation between the duration of snuff use and risk for cancer, as well as a striking localization of the carcinogenicity to the gum and buccal mucosa (table 6). For long-term chronic users of snuff, there was nearly a fiftyfold increase in risk for cancers of the gum and buccal mucosa. Indeed, almost all of the patients with cheek and gum cancers had dipped snuff.

TABLE 6.—Estimated Relative Risk of Oro-Pharyngeal Cancer According to Duration of Snuff Use and Anatomic Site, Winn et al. *(21)*

Anatomic Site	Duration of Snuff Use (yr)	Relative Risk Estimate	95%-Confidence Interval
Gum and Buccal Mucosa	0	1.0	—
	1 – 24	13.8	1.9 – 98
	25 – 49	12.6	2.7 – 53
	≥ 50	48.0	9.1 – 250
Other Mouth and Pharynx	0	1.0	—
	1 – 24	1.7	0.4 – 7.2
	25 – 49	3.8	1.5 – 9.6
	≥ 50	1.3	0.5 – 3.2

Although some of the exposure information came from interviews with next of kin, when the analysis was restricted to interviews with study subjects, the association between snuff and oral cancer was even stronger *(39)*. Matched conditional logistic analysis yielded similar results *(39)*. Based on calculations of attributable risk, the authors estimated that 87 percent of these cancers were due to the patients' snuff-dipping habits. The authors also provided data that demonstrated the negative confounding by tobacco smoking in the population, raising the possibility of a serious validity problem with the other studies that did not control for smoking. If the negative correlation between the use of smokeless and smoked tobacco holds in other populations, estimates of the carcinogenic effect of smokeless tobacco in studies without the control of smoking may be underestimates. The quantitative information that was provided by the Winn et al. study led its authors to conclude that the long-standing use of smokeless tobacco by Southern women was the principal cause of the elevated mortality from oral cancer among women in the Southern United States.

Cohort Studies

Few cohort studies of smokeless tobacco have been undertaken because of the rarity of both the exposure (smokeless tobacco use) and the outcome (oral cancer) of most interest. Bjelke and Schuman *(40)* reported on cancer mortality in cohorts of 12,945 Norwegian men and 16,930 American men and found increases in the risk of death for cancers of the buccal cavity, pharynx, and esophagus (relative risk estimates ranged from 2.6 to 3.1 *(41)*; no further detail was given). They noted a negative association between smoking and chewing tobacco, confirming the pattern that was observed from the case-control research. In a 16-year followup of U.S. veterans, Winn et al. reported no deaths from oral or pharyngeal cancer among 951 smokeless tobacco

users who did not use other forms of tobacco (about 0.5 deaths were expected) but a significant increase in both oral and pharyngeal cancers among smokeless tobacco users who were light smokers *(42)*. These data, as well as those from Bjelke and Schuman *(40)*, were reported only as abstracts in scientific journals or proceedings, with little or no detail as to the methods used, hindering interpretation of the results.

Smith and colleagues followed a group of about 1,500 patients with changes in the oral mucosa to evaluate the effects of smokeless tobacco use *(43,44)*. No oral cavity cancers were found in about 16,000 person-years of followup. Based on the results of other studies, two or three should have been detected over the study period. Smith gave little documentation of the methods that were employed for followup; however, 12 percent of the original group (201 subjects) were lost without any data on outcome, and there was apparently no effort to trace them. It seems likely that persons who died and persons who developed cancer, including some with tumors of the oral cavity, may have been lost to followup. In fact, no deaths among cohort members were reported, whereas perhaps as many as 100 or more would have been expected among such a cohort of middle-aged adults, making Smith's data uninterpretable.

Data From Asia

The highest rates of oral cancer among the more than 100 that are listed from population-based registries around the world that report standardized cancer incidence statistics are found in India *(45)*. In many areas of Asia, hospital statistics suggest that oral cancer is extremely common and often accounts for 25 or more percent of all cancers *(46-49)*, proportions that are far greater than in most areas of the United States where oral cancers typically comprise only 3 percent of all malignancies *(3)*. It has long been thought that the chewing of quids that contain tobacco and other substances is the cause of the increased risk of oral cancer in these areas *(50)*.

The smokeless tobacco products that are commonly used include tobacco with betel leaf, areca nut, and lime mixtures (often referred to as "pan"); Khaini (powdered tobacco and slaked lime paste); mishri (powdered, partially burnt black tobacco); nass (tobacco, ash, and cotton or sesame oil; lime is used in Iran and certain Soviet Republics); and various preparations that vary locally throughout the Southeast Asia region.

The inclusion of lime, areca nut, and other ingredients in many of the smokeless tobacco-containing quids hinders the evaluation of the contribution of tobacco per se to the increased risk of oral tumors. From five investigations, however, relative risks of oral cancer among chewers of betel quids with versus without tobacco can be calculated. Data from these case-control studies, which were conducted in Calcutta, Madras, Karachi, Bombay, and several parts of India and Sri Lanka *(47,51-55)*, reveal considerably higher risks of oral cancer for the

TABLE 7.—Relative Risk of Oral Cancer From Betel Quid With and Without Tobacco (With 95-Percent Confidence Limit)

Study Location (References)		Betel Quid With Tobacco	Betel Quid Without Tobacco	No Chewing Habit	Remarks
Calcutta, India *(50,54)*	Cases	138	46	135	Smokers not included in these data. Only buccal mucosa cancers considered.
	Controls	61	70	256	
	Relative risk estimates	4.3 (3.0-6.1)	1.2 (0.8-1.9)		
Madras, India *(51,54)*	Cases	219	33	25	Smokers not included in these data. Only buccal mucosa and tongue cancer cases included. Numbers reconstructed from percentages and totals.
	Controls	35	144	99	
	Relative risk estimates	25 (15-41)	0.91 (0.4-1.6)		
Karachi, Pakistan *(52,54)*	Cases	339	40	88	Smokers not included in these data.
	Controls	474	216	1,690	
	Relative risk estimates	14 (11-17)	3.6 (2.4-5.2)		
Bombay, India *(53)*	Cases	238	44	129	Separate analyses indicate that elevated risks of oral cancer associated with tobacco chewing are found among nonsmokers as well as smokers.
	Controls	513	152	1,340	
	Relative risk estimates	4.8 (3.9-6.0)	3.0 (2.1-4.3)		
India and Sri Lanka *(47)*	Cases	120	3	6	Smokers not included in these data. Only buccal mucosa cancer considered.
	Controls	63	8	47	
	Relative risk estimates	15 (7.0-32)	2.9 (0.6-14)		

use of tobacco-containing compared to nontobacco-containing quids (table 7). The findings thus suggest that the addition of tobacco contributes substantially to the elevated cancer risk among chewers, although other differences between those who use versus those who do not use tobacco-containing quids could influence the differences. Smoking, however, is not such a difference, since most of the investigations referred to in table 7 demonstrated high relative risks of oral cancer (with excesses among tobacco chewers often exceeding tenfold compared to nonquid users) among chewers who did not smoke, ruling out confounding by cigarette smoking. The studies also generally found that the large majority of oral cancer patients had been tobacco chewers and suggest that the habit of quid chewing accounts for most of the oral cancers in the diverse populations studied *(55,56)*.

Summary

Numerous case reports, especially in the South, have described oral cancers among smokeless tobacco users. The tumors often arose at anatomic locations where the tobacco was routinely placed. The number of epidemiologic investigations evaluating the relation between smokeless tobacco and oral cancer is not large, and several studies have methodologic limitations. The pattern of increased oral cancer risk among smokeless tobacco users, however, is generally consistent across studies, with evidence of an increasing risk with increasing duration of exposure, and with excess risks tending to be greatest for those anatomic sites where tobacco exposures are greatest. The best designed study was drawn from a female population in the Southern United States where exposure rates are high and potentially confounding variables could be taken into account. This study showed that chronic snuff users were at substantially increased risk of oral cancers and that nearly all tumors of the cheek and gum were due to snuff use. Evidence from parts of Asia, where the prevalence of smokeless tobacco use is high and oral cancer is the most common tumor, indicates a strong association between the chewing of quids and oral cancer. Users of quids that contain tobacco have much higher oral cancer rates than users of quids that do not, and the association is not confounded by cigarette smoking, raising the possibility that tobacco per se contributes to the elevated oral cancer risk in this part of the world. In summary, users of smokeless tobacco face a strongly increased risk of oral cancer, particularly for the tissues that come in contact with the tobacco.

References

(1) Office on Smoking and Health. Smoking and Health: A Report of the Surgeon General. U.S. Department of Health, Education, and Welfare. Washington, D.C., U.S. Government Printing Office, 1979.

(2) Blot, W.J., and Fraumeni, J.F. Geographic patterns of oral cancer in the United States: Etiologic implications. J. Chron. Dis. *30:* 745-757, 1977.

(3) Young, J.L., Percy, C.L., and Asire, A.J. Surveillance, epidemiology, and end results: Incidence and mortality data, 1973-77. NCI Monogr. *57,* 1981.

(4) Rosenfeld, L., and Callaway, J. Snuff dipper's cancer. Am. J. Surg. *106:* 840-844, 1963.

(5) Rosenfeld, L., and Callaway, J. Squamous cell carcinoma of the oral cavity. South. Med. J. *56:* 1394-1399, 1963.

(6) Landy, J.L., and White, H.J. Buccogingival carcinoma of snuff dippers. Ann Surg. *27:* 442-447, 1961.

(7) Wilkins, S.A., and Vogler, W.R. Cancer of the gingiva. Surg. Gynecol. Obstet. *105:* 145-152, 1957.

(8) Brown, R.L., Sun, J.M., Scarborough, J.E., Wilkins, S.A., and Smith, R.R. Snuff dippers intraoral cancer: Clinical characteristics and response to therapy. Cancer *18:* 2-13, 1965.

(9) Coleman, C.C. Surgical treatment of extensive cancers of the mouth and pharynx. Ann. Surg. *161:* 634-644, 1965.

(10) Fonts, E.A., Greenlaw, R.H., Rush, B.F., and Rovin, S. Verrucous squamous cell carcinoma of the oral cavity. Cancer *23:* 152-160, 1969.

(11) Hartselle, M.L. Oral carcinoma as related to the use of tobacco. Ala. J. Med. Sci. *14:* 188-194, 1977.

(12) McGuirt, W.F. Snuff dipper's carcinoma. Arch. Otolaryngol. *109:* 757-760, 1983.

(13) McGuirt, W.F. Head and neck cancer in women—a changing profile. Laryngoscope *93:* 106-107, 1983.

(14) Ahblom, H.E. Predisposing factors for epitheliomas of the oral cavity, larynx, pharynx, and esophagus. Acta Radiol. *18:* 163-185, 1937 (in Swedish).

(15) Axéll, T., et al. Snuff dipping and oral cancer—a retrospective study. Tandlakartidningen *75:* 2224-2226, 1978.

(16) Friedell, H.L., and Rosenthal, L.M. The etiologic role of chewing tobacco in cancer of the mouth. JAMA *116:* 2130-2135, 1941.

(17) Moertel, C.G., and Foss, E.L. Multicentric carcinomas of the oral cavity. Surg. Gynecol. Obstet. *106:* 652-654, 1958.

(18) Sorger, K., and Myrden, J.A. Verrucous carcinoma of the buccal mucosa in tobacco-chewers. Can. Med. Assoc. J. *83:* 1413-1417, 1960.

(19) Stecker, R.H., Devine, K.D., and Harrison, E.G., Jr. Verrucose "snuff dippers" carcinoma of the oral cavity. JAMA *189:* 838-840, 1964.

(20) Ackerman, L.V. Verrucous carcinoma of the oral cavity. Surgery *23:* 670-678, 1948.

(21) Winn, D.M., Blot, W.J., Shy, C.M., et al. Snuff dipping and oral cancer among women in the Southern United States. N. Engl. J. Med. *304:* 745-749, 1981.

(22) Rothman, K., and Keller, E. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J. Chron. Dis. *25:* 711-716, 1972.

(23) Moore, G.E., Bissinger, L.L., and Proehl, E.C. Tobacco and intra-oral cancer. Surg. Forum *3:* 685-688, 1952.

(24) Moore, G.E., Bissinger, L.L., and Proehl, E.C. Intra-oral cancer and the use of chewing tobacco. J. Am. Geriatr. Soc. *1:* 497-506, 1953.

(25) Wynder, E.L., Hultberg, S., Jacobsen, F., and Bruss, I.J. Environmental factors in cancer of the upper alimentary tract. Cancer *10:* 470-487, 1957.

(26) Wynder, E.L., Bruss, I.J., and Feldman, R.M. A study of the etiological factors in cancer of the mouth. Cancer *10:* 1300-1323, 1957.

(27) Peacock, E.E., Greenberg, B.G., and Brawley, B.W. The effect of snuff and tobacco on the production of oral carcinoma. Am. Surg. *151:* 542-550, 1960.

(28) Vogler, W.R., Lloyd, J.W., and Milmore, B.K. A retrospective study of etiological factors in cancer of the mouth, pharynx, and larynx. Science *15:* 246-258, 1962.

(29) Vincent, R.G., and Marchetta F. The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx, or larynx. Am. J. Surg. *106:* 501-505, 1963.

(30) Martinez, I. Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. J. Natl. Cancer Inst. *42:* 1069-1094, 1969.

(31) Williams, R.R., and Horm, J.W. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey. J. Natl. Cancer Inst. *58:* 525-547, 1977.

(32) Browne, R.M., Camsey, M.C., Waterhouse, J.A.H., and Manning, G.L. Etiological factors in oral squamous cell carcinoma. Community Dent. Oral Epidemiol. *5:* 301-306, 1977.

(33) Westbrook, K.C., Sven, J.Y., Hawkins, J.M., and McKinney, D.C. Snuff dipper's carcinoma: Fact or fiction? In: H.E. Nieburg (ed). Prevention and Detection of Cancer. New York, Marcel Dekker, 1980, pp. 1367-1371.

(34) Wynder, E.L., and Stellman, S.D. Comparative epidemiology of tobacco-related cancers. Cancer Res. *37:* 4608-4622, 1977.

(35) Wynder, E.L., Kabat, G., Rosenberg, G., and Levenstein, M. Oral cancer and mouthwash use. JNCI *70:* 255-260, 1983.

(36) Winn, D.M., Blot, W.J., and Fraumeni, J.F. Snuff dipping and oral cancer. N. Engl. J. Med. *305:* 230-231, 1981.

(37) Winn, D.M., Ziegler, R.G., Pickle, L.W., Gridley, G., Blot, W.J., and Hoover, R.N. Diet in the etiology of oral and pharyngeal cancers among women from the Southern United States. Cancer Res. *44:* 1216-1222, 1984.

(38) Blot, W.J., Winn, D.M., and Fraumeni, J.F. Oral cancer and mouthwash. JNCI *70:* 251-253, 1983.

(39) Winn, D.M. Smokeless tobacco and oral-pharynx cancer: The role of cofactors. Banbury Report (in press).

(40) Bjelke, E., and Schuman, L.M. Chewing tobacco and use of snuff: Relationships to cancer of the pancreas and other sites in two prospective studies. Proceedings of the 13th International Congress on Cancer, 1982, p. 207.

(41) International Agency for Research on Cancer. Tobacco habits other than smoking: Betel-quid and areca-nut chewing; and some related nitrosamines. IARC Monogr. Eval. Carcinog. Risk Chem. Hum. *37:* 103-104, 1985.

(42) Winn, D.M., Walrath, J., Blot, W., and Rogot, E. Chewing tobacco and snuff in relation to cause of death in a large prospective cohort (Abstract). Am. J. Epidemiol. *116:* 567, 1982.

(43) Smith, J.F., Mincer, H.A., Hopkins, K.P., and Bell, J. Snuff-dippers lesion: A cytological and pathological study in a large population. Arch. Otolaryngol. *92:* 450-456, 1970.

(44) Smith, J.F. Snuff dippers lesion, a ten-year follow-up. Arch. Otolaryngol. *101:* 2767-277, 1975.

(45) Waterhouse, J., Muir, C., Shanmugaranam, K., and Powell, J. Cancer incidence in five continents, Vol. IV. Lyon, France, International Agency for Research on Cancer, 1982.

(46) Pindborg, J.J. Epidemiologic studies of oral cancer. Int. Dent. J. *27:* 172-178, 1977.

(47) Wahi, P.N. The epidemiology of oral and oropharyngeal cancer. Bull. WHO *38:* 495-521, 1968.

(48) Hirayama, T. An epidemiologic study of oral and pharyngeal cancer in Central and Southeast Asia. Bull. WHO *34:* 41-69, 1966.

(49) Paymaster, J.C. Cancer and its distribution in India. Cancer *17:* 1026, 1964.

(50) Orr, I.M. Oral cancer in betel nut chewers in Travancore. Lancet *2:* 575-580, 1933.

(51) Chandra, A. Different habits and this relation with cheek cancer. Bull. Cancer Hosp. Natl. Cancer Res. Center *1:* 33, 1962.

(52) Shanta, V., and Krishnamurthi, S. A study of aetiological factors in oral squamous cell carcinoma. Br. J. Cancer *13:* 381, 1959.

(53) Jafary, N.A., and Zaidi, S.H. Carcinoma of the oral cavity in Karachi, Pakistan: An appraisal. Trop. Doct. *6:* 63, 1976.

(54) Jussawalla, D.J., and Deshpande, V.A. Evaluation of cancer risk in tobacco chewers and smokers: An epidemiologic assessment. Cancer *28:* 244-252, 1971.

(55) Gupta, P.C., Pindborg, J.J., and Mehta, F.S. Comparison of carcinogenicity of betel quid with and without tobacco. An epidemiological review. Ecol. Dis. *1:* 213-219, 1982.

(56) Jayant, K., Balakrishnan, V., Sanghvi, L.D., and Jussawalla, D.J. Quantification of the role of smoking and chewing tobacco in oral, pharyngeal, and esophageal cancers. Br. J. Cancer *35:* 232-235, 1977.

EPIDEMIOLOGIC STUDIES OF OTHER CANCERS IN RELATION TO SMOKELESS TOBACCO USE

The epidemiologic studies reported in the preceding section that show an association between the use of smokeless tobacco and oral cancers, particularly malignancies of the cheek and gum, indicate that the topical exposure of tissues to tobacco can cause cancers at the site of the exposure. In the United States, the tissues in direct prolonged contact with the tobacco are generally those of the oral cavity. Smokeless tobacco may occasionally come in contact with other tissues. One case has been reported of squamous cell carcinoma that developed in the ear of an individual in Minnesota who habitually placed snuff in his ear for 42 years at the site where the neoplasm developed *(1)*. Although but a single report, this highly unusual observation raises the possibility of a carcinogenic potential of smokeless tobacco at other anatomic sites when exposure is direct and prolonged.

Nasal Cancer

In some areas of the world snuff is inhaled, so that tissues of the nasal cavity come in contact with the tobacco powder. The earliest report that links any form of tobacco to cancer was published over two centuries ago when what were probably nasal cancers were described in several patients in England who were heavy inhalers of snuff *(2)*. There have been no systematic evaluations of snuff inhalation and nasal cancer in the United States, United Kingdom, or other European countries, most likely because both the sniffing habit and nasal cancer are uncommon. Sniffing snuff has been reported, however, to be a frequent habit among Bantu men, whose rates of nasal cancer have been reported to be high *(3)*. In case-control studies of nasal sinus cancer reported in 1955, 80 percent of patients with tumors of the maxillary antrum were prolonged and heavy snuff users, in contrast to about one-third of Bantu men with other cancers *(4,5)*. The snuff used by the Bantu is thought to contain aloe plant ash, trace elements such as nickel and chromium, and other ingredients in addition to tobacco *(6)*. Snuff use (presumably by inhalation) was reported not to account for the high rates of nasal adenocarcinoma among furniture makers in studies in England and Denmark, but evaluations of snuff itself as a risk factor were not undertaken *(7,8)*.

One case-control study of cancers of the nasal cavity and paranasal sinuses in the United States addressed the issue of smokeless tobacco *(9)*. A total of 193 cases were identified in four hospitals in Virginia and North Carolina over a 10-year period. No association between sinonasal cancers and chewing tobacco was found (relative risk 0.7, 95-percent confidence interval 0.4-1.5). However, a relative risk of 1.5 was observed for users of snuff (95-percent confidence interval 0.8-2.8). Risk was increased in snuff users for both adenocarcinomas (relative risk 3.1) and squamous cell carcinomas (relative risk 1.9) but not for other histologic types (relative risk 0.6) and was found for both sexes. The implications of the findings are not clear since the snuff used by the cases and controls was oral snuff not coming in contact with nasal tissues. Animal experiments, however, suggest that tumors distant to the site of exposure may result from exposure to constituents of snuff (see the section on animal studies).

An apparent excess of posterior nasal space tumors was reported among certain tribes in Kenya, and 6 or 12 cases interviewed were found to be chronic "liquid snuff" users *(10)*. Multiple subsites of the respiratory tract were considered, however, increasing the likelihood of a chance association. No increased risk of nasopharyngeal cancer associated with snuff use was noted in a case-control study in Singapore *(11)*.

Esophageal Cancer

Other tissues that come in contact with constituents of smokeless tobacco in more dilute concentrations include the linings of the esophagus, larynx (supraglotic portion), and stomach. The results of studies of

TABLE 1.—Relative Risks of Esophageal Cancer in Persons Exposed to Chewing Tobacco and Snuff: Summary of Four Case-Control Studies

First Author	Type of Exposure	Level of Exposure	Sex	Cases		Controls		Relative Risk*
				No.	% Exposed	No.	% Exposed	
Wynder *(12)*	Chewing	Any	M	150	20	150	10	2.3
		< 10 yrs.			14		4	3.9
		≥ 10 yrs.			6		6	1.2
Williams *(24)*	Chewing or Snuff	Level 1	M	38	5.2	1,788	5.4	0.9
		Level 2			0		0	—
Wynder *(13)*	Chewing	Any	M	183	10.9	2,560	9.0	1.2
	Snuff	Any	M		4.4		2.7	1.7
Martinez *(14)*	Chewing†	Any	M	120	2.5	360	3.6	1.2
			F	59	11.9	177	7.3	2.7

* Calculated from published report if not provided by author.
† Restricted to nonsmokers.

cancers of these three sites in relation to smokeless tobacco are inconclusive. The studies are generally of limited power to detect small increases in risk, and many did not control for relevant, potentially confounding variables. However, some studies of these three cancers do show an increase in risk in relation to the use of smokeless tobacco. As shown in table 1, elevated relative risks of esophageal cancer up to twofold or higher were found in two hospital-based case-control studies in the United States involving 150 and 183 cancer patients *(12,13)* and one in Puerto Rico (described in the previous section) with 179 cases *(14)*. One of the studies by Wynder and colleagues, however, found no evidence of an increase in risk with duration of exposure, and all chewers were also smokers *(12)*. The effect of smoking was not adjusted for in the other study *(13)*. Another case-control study involving 120 black male cases of esophageal cancer was conducted in Washington, D.C. (15). Few of the cases or controls had used either chewing tobacco or snuff, suggesting that it did not contribute to the high rates of esophageal cancer observed in the area. Finally, data from a prospective (cohort) study of U.S. veterans were analyzed to determine whether mortality rates of specific diseases were increased in users of smokeless tobacco *(16)*. In the absence of smoking, the standardized mortality ratio for esophageal cancer was found to be 228, but this value was based on only one death. In a cohort study of 12,945 Norwegian and 16,930 American men followed over 10 years, the risk of esophageal cancer was reported to be significantly increased among men who used

chewing tobacco or snuff, after controlling for age, residence, and smoking habits *(17,18)*. Unfortunately, the results of both cohort studies have been published only as abstracts, so additional details are not available.

Some evidence that the chewing of quids may increase the risk of esophageal cancer arises from studies in Southeast Asia. In a series of 237 cases of esophageal cancers in Sri Lanka, interview information from 111 revealed that 90 (81 percent) habitually used betel containing tobacco leaf *(19)*. This percentage was considerably higher than the frequency of betel chewing in the general population (30 percent). Betel chewing was more common among women. Esophageal cancer also was more common among women, an unusual observation since this cancer occurs more frequently among men in almost all areas of the world that report standardized cancer statistics *(20)*. Since few women were reported to smoke or use alcohol, the possibility of an etiologic role of chewing is increased. However, the potential effects of tobacco as opposed to other ingredients in the quids cannot be distinguished. In a case-control investigation in Bombay involving interviews with 305 esophageal cancer patients and nearly 2,000 population controls of age, sex, and religions similar to all head and neck cancer cases, a 2.5-fold increased risk of esophageal malignancy was observed ($p < .01$) among nonsmokers who chewed pan, a mixture usually consisting of tobacco, betel, lime, and other ingredients *(21)*. The excess was higher, however, among those chewing quids without tobacco (relative risk 3.5) than with tobacco (relative risk 2.1). A more recent analysis *(22)* in Bombay based on 649 patients with esophageal cancer and 649 controls yielded similar qualitative findings, but the excess among users of pan without tobacco (relative risk 12.1) was accentuated compared to users of tobacco-containing chews (relative risk 2.8). On the other hand, in an earlier case-control investigation in southern India of several upper digestive tract tumors, including 93 esophageal cancers, increases in esophageal cancer risk were much greater among men who used betel with tobacco (calculated relative risk 11) than without tobacco (calculated relative risk 2) *(23)*.

The chewing of nass was not associated with esophageal cancer risk in a case-control study conducted in an area of Iran with among the world's highest rates for this cancer *(24)*. Of 638 identified cases of esophageal cancer, interviews were completed with 344 and with 2 neighborhood controls matched to each case. The relative risk associated with ever using nass was 0.9, with an upper limit of the 95-percent confidence interval of 1.5, suggesting that any major effect of nass on the origins of this cancer could be excluded.

Laryngeal Cancer

In a case-control analysis of the interview data from the Third National Cancer Survey (TNCS), Williams and Horm compared the prior use of smokeless tobacco products (in the aggregate) in persons with a